# Asymmetric Direct α,β-Functionalization of Allenes *via* Asymmetric Carbopalladation

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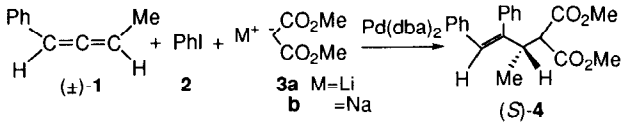
Asymmetric direct α,β-functionalization of allenes with chiral phosphine ligands was successfully achieved with extremely high enantioselectivity *via* asymmetric carbopalladation to the racemic allenes. The same palladium-catalyzed alkylation of a chiral allene was executed with complete enantiospecificity. The stereochemistry of this reaction was determined and the mechanism of this asymmetric induction is proposed.

Allene compounds have received much attention for functionalization of molecules with palladium catalysts as a carbon-three unit and have been widely used in organic synthesis.[1] Especially much interest has been placed on the stereochemistry of the palladium-catalyzed reactions in recent years.

We wish to demonstrate herein asymmetric double functionalization of allenes *via* carbopalladation[2] with chiral phosphine ligands and provide the rationalization of the reaction mechanism on the basis of the stereochemical results obtained. The palladium-assisted asymmetric α,β-functionalization of allenes with chiral ligands was realized by the initial β-phenyl–α–palladation of allenes followed by nucleophilic substitutions of chiral π–allylpalladium complexes produced subsequently.




**Scheme 1.**

**Table 1.** Asymmetric induction in the carbopalladation of allenes using chiral phosphine ligands[a]

| Ligands | Solvent | Yield of **4** (%) | e.e. of (*S*)-**4**[d] (%) |
|---|---|---|---|
| (*S*)-BINAP | THF | 33 | 88 |
| (*S*)-BINAP | THF | 34[b] | 37 |
| (*S*)-BINAP | DME | 64 | 69 |
| (*S*)-BINAP | DMSO | 42[c] | 96 |
| (*S*)-BINAP | DMSO | 75 | 89 |
| (-)-DIOP | THF | 43 | 55 |
| (-)-DIOP | DME | 54 | 72 |
| (-)-DIOP | DMSO | 76 | 80 |
| (+)-MOD-DIOP | THF | 29 | 68 |
| (+)-MOD-DIOP | DME | 38 | 67 |
| (+)-MOD-DIOP | DMSO | 89 | 90 |

[a]The reactions of (±)-**1** with **2** (1.5 equiv.) and **3b** (prepared by treating dimethyl malonate (1.2 equiv.) with NaH (1.3 equiv.)) were carried out at 66 °C for 18 h in the presence of $Pd(dba)_2$ (0.04 equiv.) and phosphine ligands (0.04 equiv.). [b]The lithium malonate **3a** generated by treating with *sec*-butyllithium was used. [c]Reacted at 40 °C for 24 h. [d]The e.e. of the product **4** was determined by HPLC analysis with chiralcel OD (2-propanol-hexane 1:20).

The palladium-catalyzed asymmetric reactions of racemic allene, (±)-**1**, with iodobenzene (**2**) and nucleophile (malonate carbanion (**3**)) were studied by using (4*R*,5*R*)-(-)-DIOP, (4*R*,5*R*)-(+)-MOD-DIOP or (*S*)-(-)-BINAP as a ligand. The reactions of (±)-**1**with **2** (1.5 equiv.) and lithium or sodium malonate (**3a,b**) were carried out in the presence of $Pd(dba)_2$ (0.04 equiv.) and chiral phosphine ligands (0.04 equiv.) described above in THF, DME, or DMSO to give (*S*)-**4**. The geometry of the olefin in the product **4** was determined as *cis* configuration between the two phenyl groups by the observation of the NOE between the olefinic hydrogen and the methyl and the hydrogen groups at the chiral carbon center in the NMR spectral analysis. The enantiomeric excess of the product **4** was determined by HPLC analysis with chiralcel OD. The results obtained are summarized in Table 1. The use of **3b** as nucleophile provided much higher enantioselectivity than the lithium enolate (**3a**). The dramatic solvent effects on the enantioselectivity were observed. The reaction of (±)-**1** with **2** and **3b** in DMSO at 40 ℃ produced (*S*)-**4** with highest e.e. (96%).

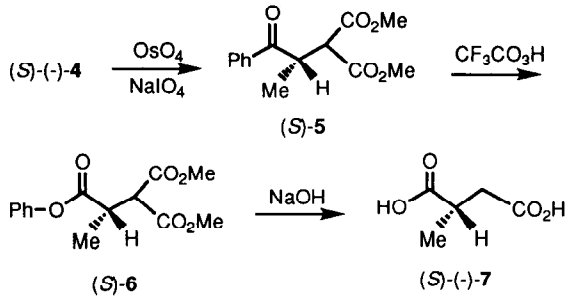
The palladium-catalyzed asymmetric reactions of (±)-**1** were carried out with ferrocenyl ligands, (*R*)-(*S*)-BPPFOAc, or (*R*)-(*S*)-PPFOMe,[3] providing (*S*)-**4** and the results are listed in Table 2. With these ligands, the severe solvent effects were also observed; the reaction in DMSO provided the highest enantioselectivity (95%).

**Table 2.** Asymmetric induction in the carbopalladation of allenes using chiral ferrocenyl phosphine ligands[a]

| Ligands | Solvent | Yield of **4** (%) | e.e. of (*S*)-**4**[b] (%) |
|---|---|---|---|
| (*R*)-(*S*)-PPFOMe | THF | 36 | 56 |
| (*R*)-(*S*)-PPFOMe | DME | 37 | 53 |
| (*R*)-(*S*)-PPFOMe | DMSO | 49 | 80 |
| (*R*)-(*S*)-BPPFOAc | THF | 51 | 36 |
| (*R*)-(*S*)-BPPFOAc | DME | 75 | 65 |
| (*R*)-(*S*)-BPPFOAc | DMSO | 77 | 95 |

[a]The reactions of (±)-**1** with **2** (1.5 equiv.) and **3b** (prepared by treating dimethyl malonate (1.2 equiv.) with NaH (1.3 equiv.)) were carried out at 66 °C for 18 h in the presence of $Pd(dba)_2$ (0.04 equiv.) and phosphine ligands (0.04 equiv.). [b]The e.e. of the product **4** was determined by HPLC analysis with chiralcel OD (2-propanol-hexane 1:20).

The absolute configuration of the newly created asymmetric carbon in the afore-mentioned asymmetric synthesis was determined by the chemical correlation to a known compound as follows. The oxidative cleavage of the carbon-carbon double bond of (-)-**4** with $OsO_4$-$NaIO_4$ followed by Baeyer-Villiger oxidation of **5** obtained with $CF_3CO_3H$ and hydrolytic decarboxylation of **6** gave (*S*)-(-)-**7** of known absolute configuration.[4] Accordingly, the absolute configuration of the product **4** obtained above was determined as (*S*)-(-).

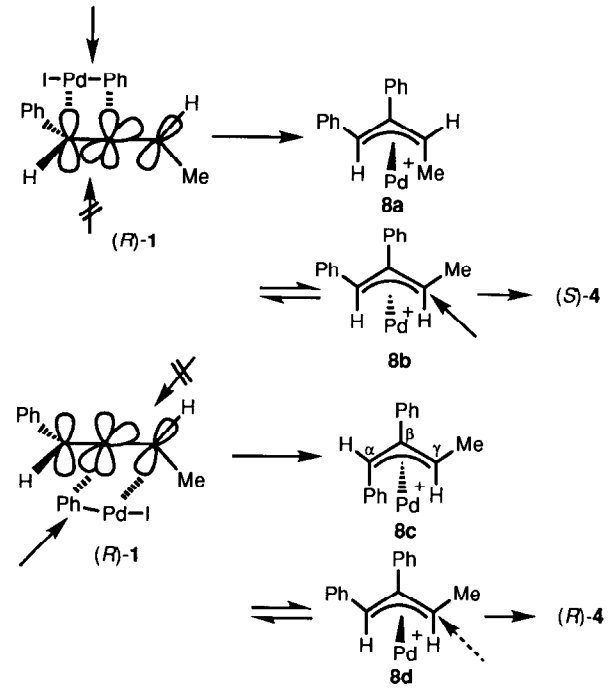



Scheme 2.

This palladium-catalyzed reaction was applied to chiral allene systems. A chiral allene (*R*)-**1**, prepared by the known method[5] *via* the stereospecific nucleophilic substitution of (*S*)-1-methylpropargyl methanesulfonate with phenylmagnesium bromide, was reacted with **2** (1.5 equiv.) and **3b** (1.2 equiv.) in the presence of $Pd(dba)_2$ (0.04 equiv.) and dppe (0.04 equiv.) under reflux in THF for 18 h produced (*S*)-**4** with complete stereospecificity.

The stereochemistry of this stereospecific reaction was rationalized as follows. The carbopalladation at the methyl-substituted carbon-carbon double bond (MeCH=C) site would occur from the sterically less crowded hydrogen side as depicted in Scheme **3** to give π–allylpalladium complex **8c**. However, the rather severe steric hindrance would exist between the phenyl (α) and the hydrogen (γ) groups in the π–allylpalladium system **8c**. Therefore, the carbopalladation at the carbon (β)-carbon (γ) double bond site (MeCH=C) would be unaccessible.

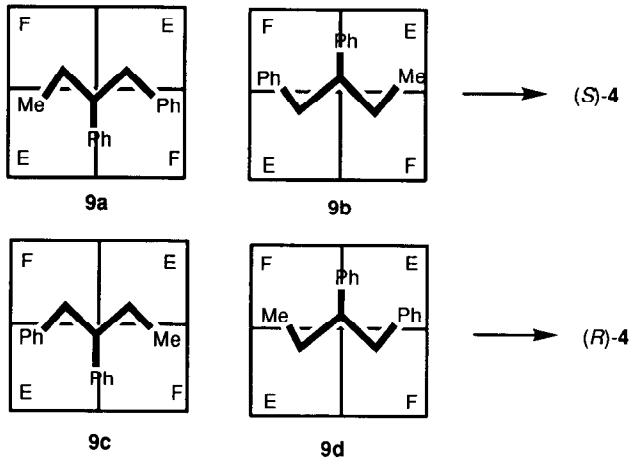
The carbopalladation of (*R*)-**1** with Ph-Pd-I at the phenyl-substituted carbon-carbon double bond (Ph-CH=C) site would preferentially occur from the sterically less crowded hydrogen side to form sterically rather preferred π–allylpalladium complex **8a** which would isomerize to the more stable isomer **8b** with




Scheme 3.

retaining of the chirality of the π–allylpalladium induced by the chirality of the starting chiral allene. The nucleophilic substitution of **8a** or **8b** with malonate carbanion **3** from the back side of the palladium catalyst would produce (*S*)-**4**.

The mechanism of the asymmetric induction in the carbopalladation of the allene with chiral phosphine ligands is rationalized as follows. As mentioned above, the result with chiral allene (*R*)-**1** indicates that the palladium-catalyzed reactions of (±)-**1** with chiral phosphine ligands would form a sterically preferred stable (less reactive) π-allylpalladium intermediate, presumably *via* diastereomeric equilibrium, which has chiral environment induced by chiral phosphine ligands. In the case of chiral ligands, (*S*)-BINAP, (-)-DIOP, and (+)-MOD-DIOP, having the same chiral environment, the sterically preferred π–allylpalladium complex **9a** and **9b** would be preferentially formed, in the four possible isomers **9a-d** (depicted a face group site as F and an edge group site as E),[6] owing to the existence of the large phenyl group in the sterically less crowded face (F) side, and reacted with the nucleophile from the back side of the palladium catalyst to give (*S*)-**4**.




Scheme 4.

Thus, it should be concluded the palladium-catalyzed asymmetric reaction of (±)-**1** with iodobenzene and nucleophile (malonate carbanion) using chiral phosphine ligands provided a direct α,β–functionalized compound with extremely high enantioselectivity, however a similar reaction of the chiral allene using an achiral phosphine ligand proceeded with complete enantiospecificity.

## References

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